Desymmetrization of meso-Dicarbonyl Compounds by the Horner-Wadsworth-Emmons Reaction (SYNTHETIC ORGANIC CHEMISTRY - Fine Organic Synthesis)

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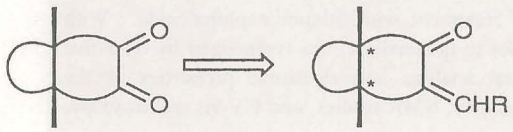
Kaoru Fuji, Kiyoshi Tanaka, Yoshihisa Ohta and Toshiyuki Watanabe

A chiral phosphonoacetate **1** differentiates the enantiotopic carbonyl groups in α-diketones to afford the *Z*- or *E*-olefin as a major product. Enantiomeric excess (ee) was generally high in *Z*-olefins.

Keywords: Asymmetric synthesis/ Horner-Wadsworth reaction/ α-Diketone/ Wittig reaction/ Binaphthol

The olefination of a carbonyl group is an unsuitable reaction for asymmetric synthesis, since it does not create a new sp^3-carbon center. An attractive entry to optically active olefins would be opened, if one of the carbonyl groups of *meso*-diketone is transformed into the carbon-carbon double bond (Scheme I). Here we describe the



Scheme I

realization of this concept by the Horner-Wadsworth-Emmons (HWE) reaction utilizing a chiral phosphonoacetate **1**. Precedents for enantioselective desymmetrization of meso-dicarbonyl compounds include the reduction of cyclic diketones with baker's yeast [1] and intramolecular aldol condensations in the presence of an amino acid [2].

The reaction of α-diketone **2** with the anion of 1 gave the *Z*-isomer **4** with 98% ee in 95% yield along with a small amount (2%) of the corresponding *E*-isomer (~30% ee). The absolute stereochemistry of **4** was unambiguously determined by an X-ray analysis of the amide **5** derived from **4**. Noteworthy features of this reaction include, i) exclusive formation of the *Z*-isomer, which is unusual for the ordinary HWE reaction, and ii) attainment of nearly 100% transfer of chirality from the phosphinate **1** to the *Z*-isomer **4**. Although we have no precise and definite rationale for the extremely high ee of the product **4** at the moment, it is clear that both the geometry of the double bond and the absolute stereochemistry are determined by a combination of the initial exo-attack of the reagent to one of the carbonyl groups of **2**. The high *Z*-selectivity in the HWE reaction could be attributed to an increase in the rate of elimination relative to that of equilibrium between the adduct and the starting material [3].

In Order to extend the scope of this reaction and to shed light on the mechanism, enantioselective olefinations of bicyclic α-diketones **3** and **6–9** were investigated. Preliminary results indicated that the *Z*-isomer was the major product in the 4, 5-substituted ketones **1**, **2**, and **6**

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Scope of research

The research interests of the laboratory include the development of new synthetic methodology, molecular recognition, and design and synthesis of biologically active compounds including functionalized DNA oligomers. Programs are active in the areas of use of chiral leaving groups for an asymmetric induction, desymmetrization of symmetrical compounds, asymmetric alkylation of carbonyl compounds based on "memory of chirality", use of binaphthalenes in the asymmetric synthesis and chiral recognition, and untitumor diterpenoids.

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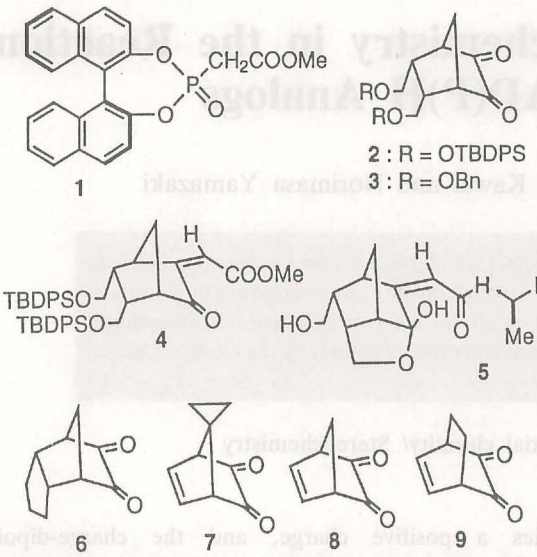


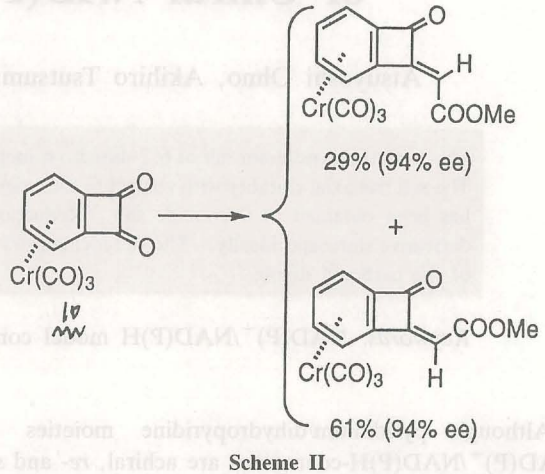
Table. *E*/*Z*-Ratio and Enantiomeric Excess of the Products

Diketone	*E*-isomer		*Z*-isomer	
	yield (%)	ee (%)	yield (%)	ee (%)
2	2	30	95	98
3	7	35	31	83
6	15	0	57	93
7	62	45	35	92
8	58	79	25	97
9	60	75	38	89

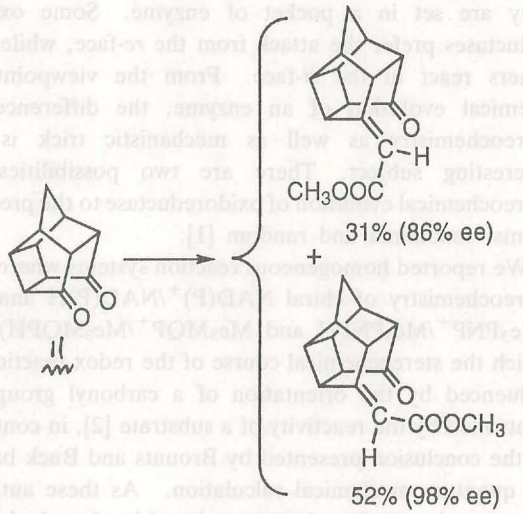
while the E-isomer was the major in $\Delta^{4,5}$-series **7–9**. The ee was generally high for *Z*-isomer (83–98% ee).

Interestingly, the phosphonate reagent 1 could discriminate the carbonyl group of a chromium complex 10 and γ-diketone 11 to afford *Z*- and *E*-isomers with high ee (Schemes II and III). The *Z*-isomer was the major product in both cases.

In conclusion, enantioselective desymmetrization of α-dicarbonyl compounds by the HWE reaction was realized for the first time. The present approach offers a simple and versatile method for the enantioselective construction of the α,β-unsaturated γ-ketoesters, which can serve as a starting material for the synthesis of optically active natural and unnatural compounds because of a highly reactive double bond.



Scheme II



Scheme III

References

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2. For a review, see: Fuji K, *Chem. Rev.*, **93**, 2037–2066 (1993).
3. Maryanoff B E and Reitz A B, *Chem. Rev.*, **89**, 863–927 (1989).